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Appendix 6

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Researchers Develop Mouse Model of Rett Syndrome

"As development progresses, what we encounter -- our experiences -- may also change how the brain responds. This may account for individual variation in disease severity," said HHMI investigator Huda Zoghbi.

July 18, 2002— By studying gene mutations in patients with the complex set of behavioral and neurological symptoms that accompany Rett syndrome, Howard Hughes Medical Institute investigator Huda Zoghbi and her colleagues at Baylor College of Medicine have designed a mouse model that faithfully recapitulates the disease down to its distinctive hand-wringing behavior.

The development of the mouse, reported in the July 18, 2002 issue of the journal *Neuron*, provides a springboard into the study of Rett syndrome, the leading cause of mental retardation in girls.

First recognized as a syndrome in the 1980s, the disorder affects one in 10,000-15,000 girls. It is particularly devastating for families with affected children because infants are seemingly normal at birth and achieve the usual developmental milestones for the first few months of life. Then, as the infant reaches toddlerhood, a sudden and dramatic decline in physical and mental capabilities takes hold, accompanied by onset of seizures, irregular breathing, awkward gait, and hand-wringing. "I know of no other neurological disease that gives this distinctive stereotypic behavior — this hand-wringing these girls do basically all the time they are awake," said Zoghbi. "With this mouse model we can now ask, 'Why is that?'"

Zoghbi has been studying Rett syndrome since the mid-1980s, when she first encountered patients with the disorder as a neurology fellow and decided to search for the gene responsible for the disorder. She reasoned that the gene must be on the X chromosome, the female sex chromosome, and it must also be essential because there had been no males reported to have the syndrome. (Since males have only one X chromosome, mutations that knock out the gene's function could be lethal at an embryonic stage.) In females, there are two copies of the X chromosome, but in each cell only one of the two X chromosomes is active. The scientists reasoned that if enough cells are "normal," they can compensate for the mutated gene.

After 14 years of searching, a scientist in Zoghbi's lab found that a gene called *MECP2* was mutated in the Rett Syndrome patients they studied. Earlier research suggested that the MeCP2 protein was responsible for making sure that genes the cell has marked with a molecular tag, called a methyl group, are silenced. The MeCP2 protein latches on to these methyl groups and prevents them from being translated into protein.

How MeCP2's molecular role translates into a neurological disorder is still not clear. Ever since a diagnostic test for the gene mutation was developed, however, there has been a flood of new information about the prevalence of the disorder. This information reveals that mutations in the *MECP2* gene can take a wide variety of forms.

"We now know of cases of classic autism and schizophrenia that are caused by mutations in this gene," said Zoghbi. "The clinical spectrum is so broad that we don't know the true prevalence of this mutation." She estimates that the mutation may be twice as common as is currently thought, with perhaps one in 10,000 children affected.

What is clear so far is that the *MECP2* gene, which resides at the end of the long arm of the human and mouse X chromosome, plays a vital role in fine-tuning the developing nervous system during a crucial stage when infants are learning to sit up, walk, and begin language acquisition, said Zoghbi.

To understand the molecular details of what goes wrong, the scientists first needed to create a mouse model of the disorder. The first attempt at a mouse model, in which the *MECP2* gene was deleted completely, resulted in severe disease and early death. Zoghbi and her colleagues sought to create a model that would more closely mimic the progression of the human disorder. So, they studied the various mutations that had been found in patients to design a mutant mouse that would produce a partially functional protein. The result was a mouse that mimics many of the aspects of the disease observed in humans.

Using the mouse model, the scientists will probe how the MeCP2 protein affects brain function at a crucial developmental stage. "The second part of the story is really in discovering what this protein is doing in the brain," said Zoghbi. "It may be that at a certain developmental stage, the brain suddenly requires the function of this protein. In humans, by birth a lot of the hardwiring has already happened. Infancy is a critical time as life experiences refine synaptic function and strengthen synapses. Experiences fine tune the brain. Perhaps more complex tasks require the input of this protein and its loss is now instrumental. Things fall apart and people regress. Perhaps key genes that are important at certain times are not put in place. We don't know the mechanism but having this mouse model will allow us to ask these questions."

Zoghbi is hopeful that studying the mouse model will also have implications for treatment of patients diagnosed with Rett Syndrome. "As development progresses, what we encounter — our experiences — may also change how the brain responds. This may account for individual variation in disease severity," she said. "It may be that enrichment of the environment or exposure to certain stimuli may give affected children more milestones. I could envision that with interventional studies in mice, we may identify pathways that could lead to behavioral or pharmacological approaches that may provide at least symptomatic relief."

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